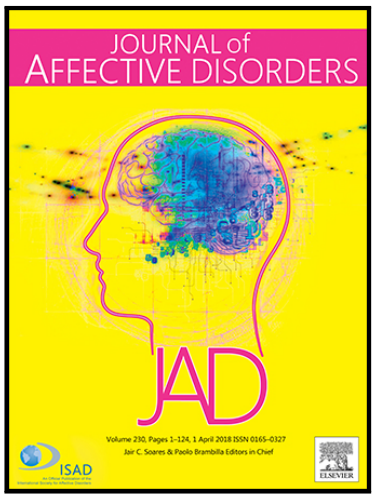

'Cool' and 'Hot' Executive Functions in suicide attempters with Major Depressive Disorder

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PII: S0165-0327(17)32182-1
DOI: 10.1016/j.jad.2018.04.057
Reference: JAD 9712

To appear in: *Journal of Affective Disorders*

Received date: 21 October 2017
Revised date: 9 March 2018
Accepted date: 5 April 2018

Please cite this article as: Ming-Chou Ho , Yi-Chieh Hsu , Mong-Liang Lu , Michael Gossop , Vincent Chin-Hung Chen , 'Cool' and 'Hot' Executive Functions in suicide attempters with Major Depressive Disorder, *Journal of Affective Disorders* (2018), doi: 10.1016/j.jad.2018.04.057

Highlights

- Patients with MDD have increased risk of all-cause mortality.
- We addressed both cool and hot EFs in MDD suicide attempters.
- The disrupted ‘cool’ EFs were found in patients with MDD.
- MDD attempters and non-attempters performed similarly to controls in the hot EF.

Running title: Depression and Executive Functions

'Cool' and 'Hot' Executive Functions in Depressed Suicide Attempters

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Running title: Depression and Executive Functions

'Cool' and 'Hot' Executive Functions in suicide attempters with Major Depressive Disorder

Abstract

Rationale: The World Health Organization reports that, by 2030, depression is expected to be the largest contributor to disease burden. Only small proportion of patients with major depressive disorder (MDD) achieves remission and the majority of them do not achieve long-term functional recovery. One of the neuropsychological domains that have been shown to be particularly impaired in depression, is that of executive function (EF).

Objectives: We examined whether the patients with MDD with and without suicide attempts had deteriorated 'cool' EF and 'hot' EF.

Methods: The study population comprised 34 MDD attempters, 36 MDD non-attempters, and 55 healthy controls. We adopted the symmetry span task (SSPAN) to measure the updating and the affective shifting task (AST) to measure the inhibition and set-shifting in general and in response to emotional material. The Iowa gambling task (IGT) was used to examine the affective decision-making ability.

Results: After controlling for PHQ-9, **Anxiety (HADS),** suicidal ideation, education year and gender, we reported that (1) the MDD non-attempters had worse updating than the healthy controls and the MDD attempters; (2) the MDD attempters had worse **general inhibition (GI)** than the healthy controls and the MDD non-attempters; (3) the MDD non-attempters had worse **general set-shifting (GS)** than the healthy controls and the MDD attempters; (4) there was no between-group difference in the 'hot' EFs; and (5) MDD attempters with longer durations (over 5 years) since last attempt had worse general inhibition.

Conclusions: The disrupted ‘cool’ EFs patients with MDD are consistent with previous review and meta-analytic studies. On the other hand, the two groups with MDD performed similarly to the healthy controls in the ‘hot’ EF.

Keywords: MDD; suicide; updating; inhibition; set-shifting; decision-making

The World Health Organization reports that, by 2030, depression is expected to be the largest contributor to disease burden (WHO, 2012). In patients with major depressive disorder (MDD), previous studies reported an increased risk of all-cause mortality, with a suicide mortality about 20 times that of the general population (Osby et al., 2001). Only approximately 30% of patients with MDD achieve remission after an adequate trial with a standard antidepressant, and the majority of individuals do not achieve long-term functional recovery (Carvalho et al., 2014). One of the neuropsychological domains that have been shown to be particularly impaired in depression, is that of executive function (EF) (Bortolato et al., 2014; Hasselbalch et al., 2011; Roiser and Sahakian, 2013; Snyder, 2013; Snyder et al., 2015).

We asked whether the patients with MDD with and without suicide attempts had deteriorated 'cool' EF and 'hot' EF (Noël et al., 2013; Tsermentseli and Poland, 2016; Zelazo et al., 2005). This issue is important because very few studies adopted a framework consisting of both 'cool' and 'hot' EFs to examine MDD suicide attempters. Most studies usually reported 'cool' EF in the attempters. Also, the three core components of 'cool' EF (updating, inhibition, and set-shifting)(Miyake et al., 2000) contribute differentially to performance on commonly used executive tasks (e.g., shifting contributes to performances of Wisconsin Card Sorting Test, WCST) (Miyake et al., 2000).

EF refers to a set of self-regulatory cognitive processes that are essential for adaptive behavior (Barkin, 2013; Pannacciulli et al., 2006). EF can be conceptualized as the integration of 'cool' EF and 'hot' EF (Noël et al., 2013; Tsermentseli and Poland, 2016; Zelazo et al., 2005). 'Cool' EF is mediated by lateral inferior and dorsolateral frontostriatal and frontoparietal networks (Kerr and Zelazo, 2004), and refers to relatively abstract, non-affective operations (Miyake et al., 2000; Zelazo et al., 2005). We adopted Miyake et al.'s (2000) influential three-component 'cool' EF model (updating, inhibition, and set-shifting) as primary research framework. Updating function requires actively manipulating relevant information in working memory, rather than passively storing information (Morris and Jones, 1990). Inhibition refers to the ability effectively to inhibit the processing of previously relevant or irrelevant

distracting information (Logan et al., 1984). The set-shifting function concerns the ability to shift back and forth between multiple tasks, operations or mental sets (Monsell, 1996). Miyake et al. (2000), suggesting that these three functions are separable but moderately correlated constructs, thus indicating both unity and diversity of EFs. 'Hot' EF is mediated by paralimbic orbitomedial and ventromedial frontolimbic structures, and refers to motivationally significant affective operations (Bechara et al., 2005; Damasio et al., 1996; Zelazo et al., 2005). The tasks used to measure 'hot' EF include the cool cognitive tests that are adapted to include emotionally valenced stimuli (Zelazo et al., 2005) and the task measuring affective decision-making (e.g., Iowa Gambling Task; IGT) (Roiser and Sahakian, 2013).

Many have shown that patients with MDD have impaired EF (Bortolato et al., 2014; Cotrena et al., 2016a; Rock et al., 2014; Roiser and Sahakian, 2013; Samamé et al., 2017; Snyder, 2013). For example, Snyder's (2013) meta-analysis demonstrated that MDD is reliably associated with impaired performance on neuropsychological measures of EF (Cohen's *d* effect sizes ranging from 0.32 to 0.97). The EF included in her meta-analytic study only included 'cool' EF, but not 'hot' EF. Rock et al.'s (2014) meta-analysis showed the presence of moderate deficits in the domains of 'cool' EF, attention and memory in patients with depression. All participants in their meta-analytic study were assessed with one single neuropsychological battery (i.e., the Cambridge Neuropsychological Test Automated Battery). Bortolato et al.'s systematic review suggested that the neuropsychological deficits (e.g., 'cool' EF in their review) are stable markers of MDD (Bortolato et al., 2014). Roiser and Sahakian's extensive review on 'cool' and 'hot' EFs in depression suggested that depressed individuals have deficient 'cool' EFs and negatively biased emotional perception and expectation (Roiser and Sahakian, 2013). More recent studies including the **qualitative** review and meta-analytic studies have also shown consistent pattern of impaired 'cool' EF in depressed individuals (Cotrena et al., 2016a; Cotrena et al., 2016b; Samamé et al., 2017; Szmulewicz et al., 2017).

'Cool' EF dysfunction has been reported in depressed individuals with suicide attempts (Bredemeier and Miller, 2015; Keilp et al., 2013; Keilp et al., 2001; Richard-Devantoy et al., 2014). For

example, Keilp et al. (2001) reported several neuropsychological deficits when comparing unmedicated patients with major depressive episode (MDE) with/out suicide attempts with the healthy controls. They reported that depressed high-lethality attempters performed worse than all groups in several tests measuring 'cool' EF ('hot' EF not tested). Keilp et al. (2013) reported that unmedicated attempters with MDE performed worse than the non-attempters and the healthy controls in many 'cool' EF (e.g., attention and working memory). Richard-Devantoy et al.'s meta-analysis showed that suicide attempters with mood disorders performed worse in IGT, category verbal fluency and the Stroop task than the non-attempters and the healthy controls (Richard-Devantoy et al., 2014). Bredemeier and Miller's review reported that studies (only measured the 'cool' EFs) including participants with unipolar depressive disorder had large proportion reporting positive results in EF deficits and suicidality (Bredemeier and Miller, 2015). Together, it appears that 'cool' EF deficits have been reported in depressed attempters.

Disadvantageous IGT performance in suicide attempters with mood disorders (Richard-Devantoy et al., 2014) has been shown to relate to malfunctioned encoding of abstract risk in the brain areas related to 'hot' EFs (e.g., ventromedial frontolimbic cortex) (Jollant et al., 2011). In addition to impaired decision-making, biased attention to emotionally valenced stimuli has been reported in depressed individuals (Roiser and Sahakian, 2013). For example, in affective Go/No-go test, depressed patients responded more quickly to name the sad words than the happy words (Erickson et al., 2005), showing a negatively biased pattern of responding. Given the deficient 'hot' EFs reported in depressed individuals, we hypothesized that the two MDD groups may have disrupted 'hot' EFs.

Method

Participants

One hundred and sixty one participants were originally recruited in three years. After excluding nine participants not completing the experiment and twenty-seven participants with low accuracy rates (below 80%) in at least one tests (symmetry span task (SSPAN) and affective shifting task (AST)), the final sample comprised 125 participants. Four participants failed both tasks (one attempter, two

non-attempters, one healthy control), four failed the AST only (two attempters, one non-attempter, one healthy control), and 19 failed the SSPAN only (seven attempters, four non-attempters, eight healthy controls). Three groups were compared, including 34 MDD outpatients with history of suicide attempts (hereafter, attempters), 36 MDD outpatients without history of suicide attempts (hereafter, non-attempters), and 55 healthy controls were included in this study. Informed consent was obtained from all participants; the study was approved by the Institutional Review Board of Chiayi Chang Gung Memorial Hospital.

All participants were between 20 and 60 years-old, were native Mandarin speakers, and had normal or corrected-to-normal vision. The two MDD groups were patients with MDD who were diagnosed by staff psychiatrists at Chiayi Chang Gung Memorial Hospital and in stable mood at the time of assessment. The psychiatrists assessed the depression by clinical interview according to DSM-V criteria. All participants including health controls also underwent psychiatric assessment using the Mini-International Neuropsychiatric Interview by a trained psychiatric nurse. All patients were currently in antidepressant treatment. The MDD attempters had history of suicide attempts, and the MDD non-attempters never attempted suicide.

Exclusion criteria for the MDD patients included history of another primary mental disorder (e.g., schizophrenia) or alcohol/illicit substance use disorder during the past year, and any neurological illnesses. All healthy controls had negative history of psychiatric disorders, neurological illness or substance-use disorders, as well as negative family history of major psychiatric or neurological illnesses, and were currently not taking any prescription of psychotropic medications.

Design

We adopted the SSPAN (Unsworth et al., 2009) to measure the updating (‘cool’ EF)(Miyake et al., 2000) and theAST (De Lissnyder et al., 2010) to measure the inhibition and set-shifting in general (‘cool’ EF) and in response to emotional material (‘hot’ EF). More specifically, we computed four indexes in terms of the AST performances (De Lissnyder et al., 2010): general inhibition (GI), general set-shifting (GS), emotion-specific inhibition (EI), and emotion-specific set-shifting (ES). We adopted

the IGT (Bechara et al., 1994) to examine the affective decision-making ability ('hot' EF).

SSPAN (Unsworth et al., 2009). We adopted an automatic version of SSPAN developed by Engle's research group (Unsworth et al., 2009). In the task, participants saw geometric figures one at a time, and were asked to judge whether the two sides of a figure were vertically symmetrical. Immediately after the symmetry judgment, a matrix consisting of 4 × 4 grids was presented with one of the grids painted red. Participants needed to memorize the location of this red paint for later recall. In each trial, the symmetry judgment task and the matrix appeared alternately two to five times (set size was 2 to 5) until the participant had to point out with the mouse cursor the order that the red paint popped out on the grid. Within each trial, the red paint never appeared at the same location. The geometric figures were never repeated in the task. There were 12 formal trials, with 3 trials for each of the 4 set sizes (2, 3, 4 and 5). Credit equal to the set size was given only when the entire set was recalled correctly in serial order; otherwise, the trial was scored as a "0". The SSPAN score was the sum of these correct sets, thus ranging from 0 to 42 (= (3 × (2+3+4+5)).

IGT (Bechara et al., 1994). Over 100 trials, participants had to make a choice between four decks of cards (A, B, C, D), some of which yielded high immediate gain but larger future losses ("disadvantageous decks": A and B) and others that yielded lower immediate gain but smaller future losses ("advantageous decks": C and D). The goal of the game was to win as much as possible. We used a global outcome score which was derived from the total number of cards chosen from the advantageous decks (C & D) minus the number of cards chosen from the disadvantageous decks (A & B) as a measure of the performance. Lower score represented poorer performance. In addition to the global outcome score, we analyzed the scores across the five blocks of task trials to examine the possible decision changes during the task.

AST (De Lissnyder et al., 2010). The stimuli were faces and were taken from the Karolinska Directed Emotional Faces (KDEF)(Lundqvist et al., 1998). All faces (223 × 223 pixels) were adjusted to exclude interference of background stimuli and were colored gray. The faces were chosen based on ratings of twenty-one college students on happiness (1= not at all; 7 = completely), sadness (1= not at

all; 7 = completely), arousal (1= calm; 7 = aroused), and gender (1= male; 7 = female). Colors (dark gray or light gray) of faces were adjusted and measured by a luminance meter. Forty-eight faces (six faces for each of eight following conditions: emotion (sad or happy), gender (male or female), and color (dark gray or light gray)) were selected in formal experiment (Appendix 1). Another twenty-four faces were selected for practice (three faces for each condition).

On each trial, one white cue word ‘‘emotion’’, ‘‘gender’’ or “color” is centrally presented for 500 ms, signalling the task-relevant feature of the subsequently presented faces (Figure 1). Immediately after this cue, four faces are centrally displayed on the screen, presented in a squared grid (2 × 2 matrix) on a black background. Each face could differ on three distinct stimulus dimensions (emotion, gender, and color). Participants were instructed to detect and locate the face that differed from the others, based on the preceding cue word. They reacted by pressing the number pad (1, 3, 7, 9 for corresponding spatial locations of faces) as fast and accurately as possible.

There were four types of trials: inhibitory, control, unclassified, and repeat. Each trial type consisted of two (repeat type) or three (inhibitory, control, and unclassified types) cued dimensions/trials programmed in sequence (for description of cued dimensions for each type, see Appendix 2). The order of the cued dimensions was pseudo-random depending on the trial type. Each of the inhibitory, control and unclassified types appeared for 48 times and the repeated type appeared for 72 times. The cued dimensions (emotion, gender and color) of the last trial were presented equally often (i.e., on the 48 inhibitory trials the three cued dimensions emotion, gender or color were each presented 16 times).

Following De Lissnyder et al. (2010), we computed four indexes: GI, EI, GS, and ES (Appendix 2). All calculations were based on the responses to the last trial in the sequence (i.e., the third trial in inhibitory, control and unclassified types, and the second trial in repeated type). Only when performances in a trial set (two or three cued trials, depending on trial type) were all correct, reaction time (RT) of the last trial in this set is included in analysis. For the analyses of RTs, median scores were used, which allows maximum inclusion of observations. As De Lissnyder et al. (2010) suggested, due

to the very fast response on color and the large difference with responses on emotion and gender, we excluded from further analyses trial types where color was programmed as the last trial in the sequence.

Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). The self-reported PHQ-9 is a reliable and valid measure of depression severity. The nine items in the PHQ-9 measure the severity of depression during the recent two weeks in terms of DSM-IV criteria. Each item is scored on a scale from 0 (none) to 3 (almost every day). Higher scores (range: 0 to 27) indicate a higher severity of depression.

Hospital anxiety and depression scale (HADS) (Snaith, 2003; Zigmond and Snaith, 1983). Seven items of anxiety related questions of the hospital anxiety and depression scale (HADS) was used to evaluate the severity of anxiety. HADS is a self-rated instrument and each item had been answered by the patient on a four point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety. A score of 0 to 7 for could be regarded as being in the normal range while a score of 8 to 10 be just suggestive of the presence.

Suicidal Ideation. We assessed the participants' suicidal ideation by the MINI suicidality module (Sheehan et al., 1998). This module comprises 6 questions about suicidal ideation and behavior: (1–5) In the past month, did you 1. think you would be better off dead or wish you were dead? (1 point), 2. want to harm yourself? (2 points), 3. think about suicide? (6 points), 4. have a suicide plan? (10 points), 5. Attempt suicide? (10 points). 6. In your life, have you ever made a suicide attempt? (4 points). We summed the scores of the first three questions to indicate the extent of suicidal ideation for all participants.

Chinese version of Suicide Intent Scale (SIS). The SIS has been one of the most commonly used instruments measuring suicide intent in clinical settings (Beck et al., 1974). The SIS consists of 8 items (objective circumstances section) for interview and 7 items for self-report. The former (objective circumstances) inquires about the factual aspects of the attempt and the surrounding events. The latter (self-report section) concerns the subject's thoughts and feelings about the former, which might be more vulnerable to distortion by people with self-harm who might wish to enhance the social

desirability of suicidal behavior or exaggerate the wish to die. Each of the SIS items is rated on a 3-point Likert-type scale (0-2) with a total score of 0-30. A Chinese version of the Suicide Intent Scale is a reliable and valid instrument for use in assessing the extent of suicidal intention with acceptable cross-cultural validity and reliability (Gau et al., 2009) among cases.

Procedure

Participants were required to complete a questionnaire. After completing the questionnaire, participants first completed SSPAN, then IGT and finally AST. The study period lasted about 90 minutes.

Results

1. Participants

The demographic characteristics of participants are shown in Table 1. There was no significant age difference between the groups. **The study sample mainly represented middle-aged group.** There were between-group differences in education years, gender ratio, PHQ-9, and suicidal ideation. That is, MDD attempters had shorter education years than the healthy controls (p = .009) and the MDD non-attempters (p = .016). This shorter education year in MDD attempters may indirectly reflect larger impact on daily functioning in these people. The two MDD groups had larger scores of PHQ-9 than the healthy controls (all ps < .0001). The MDD attempters had larger PHQ-9 scores than the MDD non-attempters (p = .017). The two MDD groups had larger anxiety scores than the healthy controls (all ps < .0001). There was no anxiety score difference between the two MDD groups (p = .089). The MDD attempters had larger extent of suicidal ideation than the MDD non-attempters (p < .0001) and the healthy controls (p = .001). The MDD non-attempters may have larger extent of suicidal ideation than the healthy controls at trend level (p = .08). Regarding the antidepressants prescribed for the depressed patients, 32.9% were selective serotonin reuptake inhibitors (SSRIs), 28.6% were serotonin and norepinephrine reuptake inhibitors (SNRIs), 11.4% were agomelatine and 11.4% were poly-antidepressants. There was no difference of prescribed type of antidepressants between suicide

attempt group and non-suicide attempt group (p=0.20).

2. 'Cool' and 'hot' EFs in three groups

To examine the effect of MDD and suicide attempts on the EFs, we conducted a one-way multivariate analysis of covariance (MANCOVA) with PHQ-9, **Anxiety (HADS),** suicidal ideation, education year, and gender (0=female; 1=male) as the covariates (Table 2). The group (MDD attempters, MDD non-attempters, and healthy controls) was a between-participant independent variable. SSPAN, IGT, AST (GI, EI, GS, and ES) were dependent variables and were respectively tested with the same above-mentioned MANCOVA.

After controlling for PHQ-9, **Anxiety (HADS),** suicidal ideation, education year and gender, the between-group differences were found in SSPAN, GI and GS. Further post-hoc pairwise comparisons were controlled at alpha value at .05 using Fisher's least significant difference (LSD) test. Specifically, the MDD non-attempters had smaller SSPAN score (worse updating) than the healthy controls (***p* = .007**). The MDD attempters had worse GI (smaller scores) than the healthy controls (p =.008) and the MDD non-attempters (***p* =.030**). The MDD non-attempters had worse GS (larger scores) than the MDD attempters (***p* = .002**) and the healthy controls at trend level (***p* = .035**). In addition to the global outcome score in the IGT, we conducted **one-way repeated-measure ANCOVA** to examine the outcome scores across the five blocks of task trials to examine the possible decision changes during the task (Table 2). There were no between-group outcome score differences across the five blocks.

3. 'Cool' and 'hot' EFs in MDD attempters

For the MDD attempters, we examined the effect of number of suicide attempts (Table 3) and the duration since the more recent attempt (Table 4) on the EFs. The number of attempts were dichotomized (1=once, 2=more than once). A one-way MANCOVA was conducted with PHQ-9, **Anxiety (HADS),** suicidal ideation, education year, and gender as the covariates. The dichotomized number of attempts was a between-participant independent variable and SSPAN, IGT, AST (GI, EI, GS, and ES) were dependent variables. There were no significant between-group differences in all variables. We conducted **one-way repeated-measure ANCOVA** to examine the IGT outcome scores across the five

blocks. Again, there were no significant between-group differences.

The duration since the more recent attempt was also dichotomized (**1 = less or equal to 5 years, range = 1 to 60 months; 2 = over 5 years, range = 72 – 132 months**). We conducted the similar MANCOVA as mentioned above. We reported the significant between-group difference only in the GI. Participants with more recent attempt within 5 years had better inhibitory control than those with over 5 years. There were no other significant between-group differences. **We also conducted one-way repeated-measure ANCOVA to examine the IGT outcome scores across the five blocks. Again, there were no significant between-group differences.**

General Discussion

We hypothesized that the patients with MDD with/out suicide attempts had deteriorated 'cool' and 'hot' EFs. After controlling for PHQ-9, **Anxiety (HADS),** suicidal ideation, education year and gender, we reported that (1) the MDD non-attempters had worse updating than the healthy controls and the MDD attempters; (2) the MDD attempters had worse GI than the healthy controls and the MDD non-attempters; (3) the MDD non-attempters had worse GS than the healthy controls and the MDD attempters; (4) there was no between-group difference in the 'hot' EFs; and (5) MDD attempters with longer durations (over 5 years) since last attempt had worse general inhibition.

The impaired updating function in patients with MDD has been reported in previous studies (Keilp et al., 2013; Moritz et al., 2002; Rose and Ebmeier, 2006). Depressive individuals had slightly poorer performances (marginal significance, $p \leq .1$) than the healthy controls in the backward digit span task (Moritz et al., 2002). Using the n-back task, Rose and Ebmeier reported that the patients with MDD had slower RT and reduced accuracy rates than the healthy controls (Rose and Ebmeier, 2006). They suggested an impaired updating of information in working memory in patients with MDD. However, these studies did not report whether or not the patients had previous suicide attempts.

Recently, Keilp et al. (2013) reported that MDD attempters performed worse in the n-bask task (loads on a updating latent variable)(Miyake et al., 2000) than the healthy controls. However, we

reported comparable updating performances between MDD attempters and the healthy controls. One possibility to account for the inconsistency may be the medication status and suicide-related indexes (e.g., the time since most recent attempt). Patients in Keilp et al. were either medication free or washed out of medications for at least two weeks prior to assessment. In contrast, our patients were currently in medical treatment. Also, the average time since most recent attempt in Keilp et al. (2013) was 44.5 months, but 84.6 months in our case. Possibly, the treatment and longer suicide interval in our study may return the attempters' updating to normal.

Another possible reason for the difference between the present findings and those of previous studies is the task used to measure updating. Most other studies rely on n-back tasks or backward digit span, while the present investigation used the SSPAN to evaluate updating. The SSPAN may rely more on spatial ability; while the other tasks rely more on verbal ability. This difference in the non-executive abilities may make it difficult to interpret the results (Snyder et al., 2015). However, previous studies have shown that the updating tasks that tap different non-executive abilities may measure the same latent construct ("updating"). For example, Miyake et al. reported that the updating tasks differing in modalities (visual vs. auditory) loaded on the same factor "updating" (Miyake et al., 2000). **Redick** et al. (2012) reported that the three complex span tasks (Operation, Symmetry, and Reading Span tasks) that tap different non-executive abilities correlated strongly with each other (Redick et al., 2012). In addition, our study provided convergent evidence of deficient updating function in depressed individuals. We believe that the SSPAN should be appropriate for measuring updating. In the future, multiple tasks that measure the same latent construct are encouraged, as suggested by Snyder et al. (2015).

The MDD attempters had worse GI than the healthy controls and the MDD non-attempters. This is consistent with Keilp et al. (2013) in that the MDD attempters had worst performance (vs. the healthy controls and the MDD non-attempters) in color-word Stroop task. In this task, participants name the colors of the inks in which words are printed, requiring the capability to override the automatic response of reading the words. However, Keilp et al. did not find the between-group difference in

another inhibition-related task, the Go/No-go task (Keilp et al., 2013). Recent meta-analytic study reported impaired inhibition (Stoop task) in patients with MDD (Snyder, 2013). There are at least three forms of inhibition: inhibition of prepotent response, inhibition of competing distractors, and inhibition of proactive interference (Nigg, 2000). The Stroop task and the AST in the current study measure primarily the inhibition of competing distractors (e.g., words in Stroop task and cue dimension in the last trial in the AST), but not the other two forms. On the other hand, the Go/No-go task measures inhibition of prepotent response (e.g., inhibit an intended response on an occasional no-go distractor). Studies using intentional or directed forgetting task (inhibition of proactive interference) reported impaired inhibition of recall irrelevant words (Cottencin et al., 2008; Joormann et al., 2005). Future studies are suggested to explicate on which form of inhibition is affects in MDD patients.

The MDD non-attempters had worst GS, comparing to the healthy controls and the MDD attempters. This is consistent with the previous studies showing impaired set-shifting in patients with MDD (Bortolato et al., 2014; Heinzel et al., 2010; Mahurin et al., 2006; Must et al., 2006; Snyder, 2013). For example, using WCST (loads on a set-shifting latent variable)(Miyake et al., 2000), Must et al. reported that patients with MDD had less number of categories completed and more perseverative errors than the controls. Snyder's (2013) meta-analytic study reported worse set-shifting (WCST and the Intradimensional/Extradimensional Shift task, but not the Trail Making Test Part B; TMT-B) in patients with MDD.

However the whole picture becomes complex and inconsistent, when it comes to patients with suicide attempts. Keilp and his colleagues (Keilp et al., 2013; Keilp et al., 2001) did not find between-group differences (MDD attempters, MDD non-attempters and controls) in WCST (e.g., number of categories completed and perseverative errors) and in TMT-B. In contrast, a recent meta-analytic study (Richard-Devantoy et al., 2014) reported that patients with mood disorders and suicide attempters both had worse set-shifting capability (WCST and TMT-B) than healthy controls (no set-shifting difference between patients and attempters). Together, there appears a trend that patients with MDD have impaired set-shifting (Bortolato et al., 2014; Snyder, 2013); however, more studies are

required to examine whether this impairment also occurs in depressed suicide attempters (Richard-Devantoy et al., 2014). So far we do not have appropriate explanations for worse GS in the non-attempters than the attempters. Since few studies examined the effect of suicide history on EFs, more future studies are encouraged on this line of research.

The current study did not find the between-group differences in the 'hot' EF (EI, ES, and IGT). The former two (EI and ES) involve executive operations (inhibition and set-shifting) on emotional faces, and the IGT involves emotion-laden learning (Damasio et al., 1996). Given that both MDD and suicidal act are highly associated with emotion, the patients in calm and undisturbed mood at the time of assessment might be less vulnerable to dysfunctional emotional processing (e.g., biased attention to negative stimuli and impaired decision-making). Suicidal acts usually occur at the climax of a complex pathological process (e.g., intense negative feelings) (Van Heeringen, 2001) and several malfunctions in emotional processing (e.g., biased attention to emotional stimuli, impaired decision-making, and impaired emotional regulation) have been reported (Jollant et al., 2011). For example, depressed suicide attempters spent longer times reading the colors of suicide-related and negative words (i.e., biased attention to negative stimuli)(Becker et al., 1999; Cha et al., 2010). Depressed suicide attempters have also shown disrupted affective decision-making (Gorlyn et al., 2013; Jollant et al., 2011; Richard-Devantoy et al., 2014). In the current study, the patients in calm mood might have relatively less disrupted emotion-related processing, possibly being less vulnerable for future attempt.

For the MDD attempters, we reported that attempters with longer durations since last attempt had worse general inhibition. It appears that the duration since last attempt was related to 'cool' EF. More studies are encouraged to examine the relationship between suicide-related indexes and cognitive functions.

The effect sizes (the partial eta-squared values) reported in Table 2 were about small to medium. Similarly, meta-analytic evidence demonstrates small-to-medium effect size across EF domains in depressed individuals (Snyder et al., 2015). Interestingly, the effect size was large when it comes to compare the MDD attempters with more recent attempt within 5 years vs. over 5 years in GI (Table 4).

This may indicate that duration since last attempt is critical to account for the EF differences in MDD attempters.

Limitations and conclusions

The current study has the following limitations. Longitudinal studies are needed to address the causal relationship between mitigated 'hot' EF and future suicide attempts. In the future, multiple measures that target each component of EF are encouraged to better rule out the alternative interpretation of non-executive factors. The current study is limited in the small sample size of the attempters. In the future, larger sample size is expected to reduce the within-group heterogeneity and increase the statistical power. Also, this study is limited in long duration since last suicide attempt (average is about 7 years). This may make it less likely to examine the immediate attempt effects (e.g., shorter duration) on EFs. There is a lack of Information regarding psychotherapy. duration of illness, number of episodes, or history of psychotic symptom, Attention Deficit Hyperactivity Disorder and eating disorder.

We reported that the patients with MDD had disrupted 'cool' EFs (updating, inhibition, and set-shifting). On the other hand, the MDD attempters and non-attempters performed similarly to the healthy controls in the 'hot' EF. The tasks chosen in the current study have the advantage to tap more specific aspect of EF (e.g., inhibition, set-shifting, updating and affective decision-making). Traditional neuropsychological EF measures usually tap multiple aspects of EF; therefore unable to answer more specific aspect of EF that is critical in psychopathology (Snyder et al., 2015).

Conflict of Interest
The authors certify that there is no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations in relation to this article.

Contributors
All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript:

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Data analysis and interpretation: All authors;
Manuscript writing: All authors;

Role of the Funding Source:
The present study is supported in part by the Ministry of Science and Technology, R.O.C. (NSC 102-2314-B-040-004-MY3, MOST 105-2314-B-182-028). The funders had no role in study design, data collection, and analysis.

Acknowledgements
The authors would like to thank Health Information and Epidemiology Laboratory (CLRPG6G0041) for the comments and assistance in data analysis

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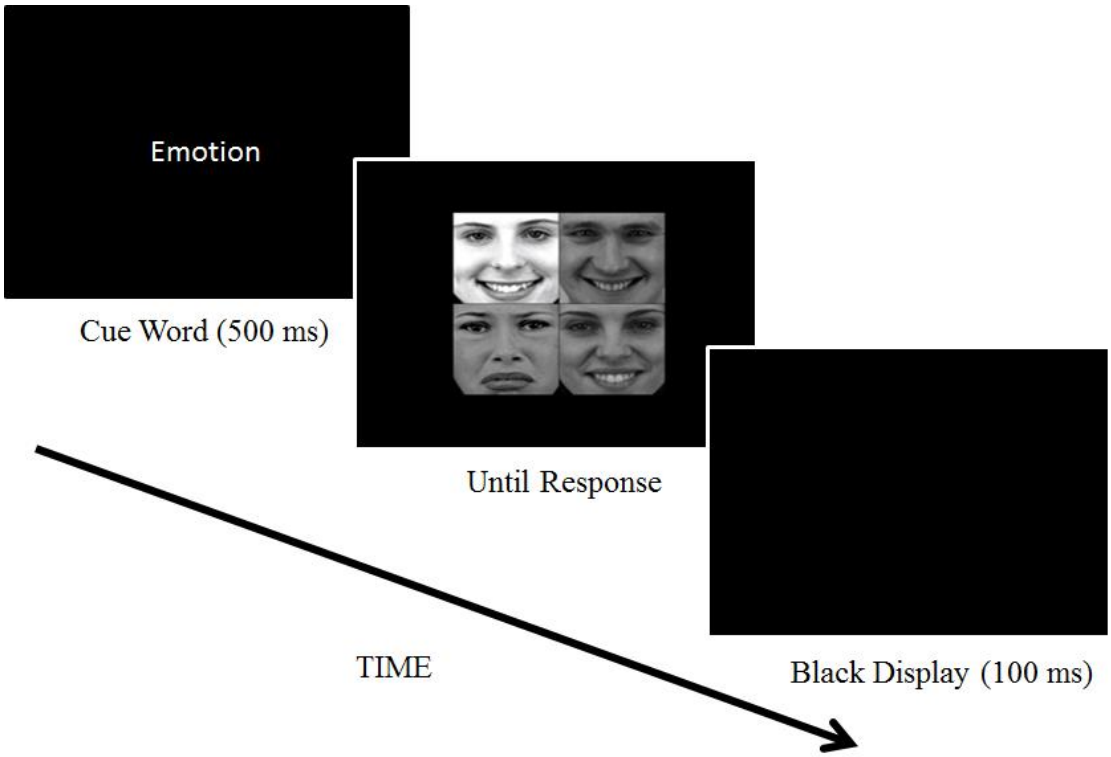

Figure 1. Example procedure in AST. In this example, participants detect and locate the emotion (the left-bottom sad face) that differed from the others (three happy faces).

Table 1. Characteristics of the MDD attempters, the MDD non-attempters, and the healthy controls (standard errors of means in parenthesis).

	MDD attempters (A) (n=34)	MDD non-attempters (N) (n=36)	Healthy controls (C) (n=55)	$F(2,122)$ or x^2	p	Contrast
Age (years)	41.8 (1.4)	43.8 (1.9)	44.3 (1.2)	.82	.442	
Education year	12.4 (0.5)	13.9 (0.4)	13.9 (0.4)	4.20	.017	N > A (p = .016) C > A (p = .009)
Female: male	31:3	20:16	46:9	14.82	.001	
PHQ-9	13.4 (1.4)	10.1 (1.1)	3.2 (0.4)	36.21	< .0001	A > C (p < .0001) N > C (p < .0001) A > N (p = .017)
Anxiety (HADS)	11.0 (.9)	9.1 (.8)	7.7 (.5)	21.5	<.0001	A > C (p < .0001) N > C (p < .0001)
Suicidal ideation	3.1 (.7)	1.0 (.4)	.1 (.1)	15.78	< .0001	A > C (p < .0001) N > C (p = .08) A > N (p = .001)
Number of attempts	2.8 [a] (3.2) Once: 17 Multiple: 17[a]					
Duration since most recent attempt (months)	84.6 (16.0)					

Suicide Intent Scale	11.5 (1.0)

a. Two patients reported multiple attempts, but did not remember the number of attempts. When computing the mean and SD of attempts, these two patients were ruled out.

***Table 2*. Adjusted means and standard errors of means (in parenthesis) of three tasks after controlling for PHQ-9, Anxiety (HADS), suicidal ideation, education year and gender.**

	MDD attempters (A) (n=34)	MDD non-attempters (N) (n=36)	Healthy controls (C) (n=55)	*F*(2,118)	*p*	*Partial η2*	Contrast
SSPAN	12.3 (1.3)	9.4 (1.2)	14.0 (1.0)	3.97	.022	.064	C > N (*p*=.007)
AST (in ms)							
General Inhibition [a]	-152.7 (64.3)	34.7 (57.0)	88.3 (50.5)	3.89	.023	.062	C > A (*p*=.008) N > A (*p*=.030)
Emotion-specific Inhibition [a]	2271.4 (143.0)	2422.7 (127.6)	1990.4 (111.8)	2.79	.065	.046	
General Set-Shifting [b]	-127.2 (132.7)	415.2 (117.7)	83.3 (103.0)	5.39	.006	.084	C < N (*p*=.035) A < N (*p*=.002)
Emotion-specific Set-Shifting [b]	863.9 (116.1)	733.8 (103.0)	513.8 (90.2)	2.42	.093	.040	
IGT	-4.0 (4.6)	5.6 (4.1)	-1.9 (3.6)	1.50	.228	.025	
Block 1	-1.9 (.9)	-1.2 (.8)	-1.7 (.7)				
Block 2	.1 (1.1)	-.0 (1.0)	.4 (.9)				
Block 3	-1.0 (1.3)	1.9 (1.2)	.2 (1.0)				
Block 4	,2 (1.7)	2.2 (1.5)	-1.0 (1.3)				
Block 5	-1.3 (1.8)	2.8 (1.6)	.3 (1.4)				

a. Higher scores reflect better inhibitory ability

b. Smaller scores reflect better set-shifting ability

SSPAN = symmetry span task. AST = affective shifting task. IGT = Iowa gambling task.

***Table 3*. Comparisons of MDD attempters with one vs. multiple attempts in SSPAN, AST and IGT. Adjusted means and standard errors of means (in parenthesis) of three tasks after controlling for PHQ-9, Anxiety (HADS), suicidal ideation,education year and gender.**

	MDD attempters		*F*(1,28)	*p*	*Partial η2*
	Once (n=17)	Multiple (n=17)			
SSPAN	13.5 (1.9)	10.1 (1.9)	.29	.597	.011
AST (in ms)					
General Inhibition [a]	-121.4 (74.7)	-1.4 (74.7)	1.06	.312	.038
Emotion-specific Inhibition [a]	2072.1 (202.3)	2322.3 (202.3)	.63	.435	.023
General Set-Shifting [b]	-233.5 (205.5)	107.0 (205.5)	.94	.342	.033
Emotion-specific Set-Shifting [b]	465.8 (164.9)	847.8 (164.9)	2.20	.149	.075
IGT	-6.0 (6.5)	-5.8 (6.5)	.000	.984	.000
Block 1	-1.5 (1.4)	-3.9 (1.4)			
Block 2	.8 (1.6)	-1.3 (1.6)			
Block 3	-2.0 (2.0)	.2 (2.0)			
Block 4	-.3 (2.5)	-2.9 (2.5)			
Block 5	-3.0 (2.3)	1.1 (2.3)			

a. Higher scores reflect better inhibitory ability

b. Smaller scores reflect better set-shifting ability

SSPAN = symmetry span task. AST = affective shifting task. IGT = Iowa gambling task.

***Table 4*. Comparisons of MDD attempters with more recent attempt within 5 years (≦5 years) vs. over 5 years (> 5 years) in SSPAN, AST and IGT. Adjusted means and standard errors of means (in parenthesis) of three tasks after controlling for PHQ-9, Anxiety (HADS), suicidal ideation, education year and gender.**

	MDD attempters		*F*(1,28)	*p*	*Partial η2*	Contrast
	Within 5 (W) (n=21)	Over 5 (O) (n=13)				
SSPAN	11.5 (1.5)	12.2 (2.0)	.06	.806	.002	
AST (in ms)						
General Inhibition [a]	37.7 (53.4)	-221.5 (68.4)	8.66	.007	.243	W > O
Emotion-specific Inhibition [a]	2303.8 (161.7)	2025.0 (207.1)	1.09	.305	.039	
General Set-Shifting [b]	138.6 (174.3)	-389.3 (223.3)	3.37	.077	.111	
Emotion-specific Set-Shifting [b]	537.2 (133.3)	850.0 (170.7)	2.02	.166	.070	
IGT	-7.6 (5.2)	-3.2 (6.7)	.26	.613	.010	
Block 1	-3.4 (1.1)	-1.6 (1.4)				
Block 2	-.7 (1.3)	.5 (1.7)				
Block 3	-1.8 (1.6)	.5 (2.0)				
Block 4	-1.6 (2.0)	-.4 (2.6)				
Block 5	-.2 (1.9)	-2.1 (2.4)				

a. Higher scores reflect better inhibitory ability

b. Smaller scores reflect better set-shifting ability

SSPAN = symmetry span task. AST = affective shifting task. IGT = Iowa gambling task.

Appendix 1. Means and standard errors of means (in parenthesis) of ratings and lightness for faces selected in the formal experiment.

	Sad faces	Happy faces	*t(20)*	*p*
Sadness	6.17 (0.52)	1.31 (0.51)	-23.96	< .0001
Happiness	1.43 (0.59)	6.51 (0.59)	22.21	< .0001
Arousal	5.59 (0.75)	5.75 (0.88)	0.93	.37

	Male faces	Female faces	*t(20)*	*p*
Gender	1.55 (0.55)	6.47 (0.56)	20.82	< .0001

	Light gray	Dark gray	*t(70)*	*p*
Lightness (cd/m^2)	146.58 (6.19)	35.34 (4.26)	88.77	< .0001

Appendix 2. Trial sequences for four types of trials, and computations of four indices.

Type	T1 → T2 → T3
Inhibitory (a→b→a)	gender → emotion (color) → gender emotion → gender (color) → emotion color → gender (emotion) → color
Control (c→b→a)	gender (color) → color (gender) → emotion emotion (gender) → gender (emotion) → color color (emotion) → emotion (color) → gender
Unclassified (b→b→a)	gender (color) → gender (color) → emotion emotion (color) → emotion (color) → gender emotion (gender) → emotion (gender) → color
Repeated (a→a)	gender → gender emotion → emotion color → color

Index	Formula	Interpretations
General Inhibition	Median RT (Inhibitory trials) – Median RT (Control trials)	Higher scores reflect better general inhibitory ability
Emotion-specific Inhibition	Median RT in T3 (emotion) – Median RT in T1 (emotion) when trial sequence is emotion → gender (color) → emotion	Higher scores reflect better emotion-specific inhibitory ability
General Shifting	[Median RT (Control) – Median RT (Unclassified)]/2 – Median RT (Repeat trials)	Smaller scores reflect better general set-shifting ability
Emotion-specific Shifting	Median RT in T2 (emotion) – Median RT in T3 (gender) in Control and Unclassified trials	Smaller scores reflect better emotion-specific set-shifting ability

Only the trial sequences (in bold) with last trial that is not color are included in analysis.